PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-33001A	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/003518	International filing date *(day/month/year)* 02.04.2004	Priority date *(day/month/year)* 04.04.2003
International Patent Classification (IPC) or national classification and IPC A61K31/498, A61K31/55, A61K45/06, A61P25/08		
Applicant NOVARTIS AG et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand 04.11.2004	Date of completion of this report 25.02.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Hornich, E Telephone No. +49 89 2399-8721

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/003518

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-12 as originally filed

   Claims, Numbers

   1-13 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 9 (with regard to industrial applicability)

because:

☒ the said international application, or the said claims Nos. 9 (with regard to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-7
	No:	Claims	1-4, 8-13
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-13
Industrial applicability (IA)	Yes:	Claims	1-8, 10-13
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

SECTION III

1. Claim 9 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

SECTION V

2. *References*:

D1: DATABASE WPI Section Ch, Week 200066 Derwent Publications Ltd., London, GB; Class B05, AN 2000-673134 & CN 1 265 889 A (WANG X) 13 September 2000 (2000-09-13)

D2: ERNST MUTSCHLER: "Arzneimittelwirkungen - Lehrbuch der Pharmakologie und Toxikologie" 1997, WISSENSCHAFTLICHE VERLAGSGESELLSCHAFT MBH STUTTGART , STUTTGART.

D3: MARK H. BEERS, M.D., ROBERT BERKOW, M.D.: "The Merck Manual" 1999, MERCK RESEARCH LABORATORIES , WHITEHOUSE STATION, N.J.

D4: DAM M: "SUMMING UP OF THE SUCCESS SO FAR GAINED THROUGH CHOICE OF DRUGS OR COMBINATIONS OF DRUGS" ACTA NEUROLOGICA SCANDINAVICA SUPPLEMENTUM, vol. 69, no. 99, 1984, pages 19-22, & 3RD WORKSHOP ON MEMORY FUNCTIONS, GOTHENBURG, FEB. 4-6, 1983. ACTA NEUROL SCAND SUPPL. ISSN: 0065-1427.

D5: US-A-5 095 033

D6: WO 89/05642 A

D7: GB 864 536 A

D8: US-A-3 489 836

D9: EP-A-0 637 449

D10: WO 01/39779 A

D11: DECKERS C L P ET AL: "Selection of antiepileptic drug polytherapy based on mechanisms of action: The evidence reviewed" EPILEPSIA 2000 UNITED STATES, vol. 41, no. 11, 2000, pages 1364-1374, ISSN: 0013-9580

D12: ZARNOWSKI TOMASZ ET AL: "NBQX: A selective AMPA antagonist enhances antiepileptic properties of common anticonvulsant drugs against maximal electroshock in mice" POLISH JOURNAL OF PHARMACOLOGY AND PHARMACY, vol. 44, no. SUPPL., 1992, pages 258-259, & XI CONGRESS OF THE POLISH PHARMACOLOGICAL SOCIETY AND OF THE GERMAN SOCIETY OF PHARMACOLOGY AND TOXI; GDANSK, POLAND; SEPTEMBER 16-19, 1992 ISSN: 0301-0244

D13: BOROWICZ KINGA K ET AL: "Interaction of GYKI 52466, a selective non-competitive antagonist of AMPA/kainate receptors, with conventional antiepileptic drugs in amygdala-kindled seizures in rats" POLISH JOURNAL OF PHARMACOLOGY, vol. 53, no. 2, March 2001 (2001-03), pages 101-108, ISSN: 1230-6002

D14: BOROWICZ KINGA K ET AL: "The non-competitive AMPA/kainate receptor antagonist, GYKI 52466, potentiates the anticonvulsant activity of conventional antiepileptics" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 281, no. 3, 1995, pages 319-326, ISSN: 0014-2999

D15: SWIADER MARIUSZ ET AL: "Influence of LY 300164, an AMPA/kainate receptor antagonist upon the anticonvulsant action of antiepileptic drugs against aminophylline-induced seizures in mice." POLISH JOURNAL OF PHARMACOLOGY, vol. 55, no. 1, January 2003 (2003-01), - February 2003 (2003-02) pages 103-107, ISSN: 1230-6002

D16: CZUCZWAR S J ET AL: "LY 300164, a novel antagonist of AMPA/kainate receptors, potentiates the anticonvulsive activity of antiepileptic drugs" EUROPEAN JOURNAL OF PHARMACOLOGY 1998 NETHERLANDS, vol. 359, no. 2-3, 1998, pages 103-109, ISSN: 0014-2999

D17: WO 02/03915 A

D18: WO 98/17692 A

D19: AUBERSON Y P ET AL: "N-phosphonoalkyl-5-aminomethylquinoxaline -2,3-diones: in vivo active AMPA and NMDA(glycine) antagonists" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 2, 18 January 1999 (1999-01-18), pages 249-254, ISSN: 0960-894X

D20: WO 03/042182 A (see **SECTION VI**)

3. *Novelty* **(Art. 33(2) PCT)**

3.1 **D1** discloses a medicament for curing epilepsy comprising phenytoin sodium, carbamazepine, primidone, sodium valproate and nitrazepam.
D1 would thus ***anticipate*** the subject-matter of claims 1-3 and 8-13.

3.2 **D2** (p. 260) discloses that valproic acid may be administered in combination with phenobarbital. Furthermore, vigabatrin and lamotrigin are described being useful as *add-on therapeutics, ie in combination with other antiepileptics.*

D2 would be ***prejudicial*** to the novelty of claims 1, 2 and 8-13.

3.3 **D3** discloses that several antiepileptics, among others gabapentin, lamotrigin or topiramate (AMPA-Antagonist) are used as *add-on drugs.*

D3 would thus be ***prejudicial*** to the ***novelty*** of claims 1-4 and 8-13.

3.4 **D4** discloses that patients were treated with combinations of (a) phenytoin and phenobarbitone, (b) carbamazepine and phenytoin and (c) carbamazepine and valproate.
D4 would **take away the novelty** of claims 1-3 and 8-13.

3.5 **D5** discloses anti-epileptic compositions containing stiripentol associated with an anti-epileptic drug. Stiripentol is known for the antiepileptic activity and was found to alleviate or prevent some major undesired effects and phenomena caused by the usual antiepileptic drugs. Stiripentol is particularly useful in the treatment of patients receiving phenytoin, carbamazepine, valproic acid or sodium valproate.

The subject-matter of claims 1-3 and 8-13 would thus ***not*** be ***novel*** with regard to **D5.**

3.6 **D6** discloses compositions comprising a dextromethorphan metabolite in combination with antiepileptics including carbamazepine, hydantoin, amobarbital sodium, methsuximide, clonazepam, valproic acid, metharbital, mephobarbital, mephenytoin, primidone, paramethadione, phenacemide and trimethadione. The metabolites of dextromethorphan themselves have anticonvulsive activity.

D6 would ***take away the novelty*** of claims 1-3 and 8-13.

3.7 **D7** discloses compositions for the treatment of epilepsy comprising d-α-ethyl-phenylacetylurea and another anticonvulsant drug (barbiturate, phenacemide, diphenylhydantoin).

The subject-matter of claims 1-2 and 8-13 would thus ***not*** be ***novel*** in view of **D7.**

3.8 **D8** describes 5-amino-10,11-dihydro-5H-dibenzo (a,d)-cycloheptenes and derivatives for the treatment of epilepsy.
The pharmaceutical compositions may additionally contain one or more known medicaments, for example phenobarbitone, 5,5-diphenylhydantoin or primidone.

D8 would ***take away the novelty*** of claims 1,2 and 8-13.

3.9 **D9** describes a pharmaceutical composition which comprises L-carnitine or a derivative thereof and a pharmacologically acceptable salt of *valproic acid* and the use thereof for the preparation of a medicament for decreasing the seizure frequency in epileptic patients.

D9 would ***anticipate the subject-matter*** of claims 1,2 and 8-13.

3.10 **D10** discloses compositions comprising levetiracetam and other antiepileptic compounds. It is described that levetiracetam, known as antiepileptic compound, potentiates the anticonvulsant activity of many antiepileptics (see p. 11, l. 26 - p. 12, l. 23; p. 15, l. 29 - p. 16, l. 20).

The subject-matter of claims 1-3 and 8-13 would ***not*** be ***novel*** in view of **D10.**

3.11 **D11** to **D17** disclose combinations of antiepileptic drugs and thus would ***take away the novelty*** of claims 1-4 and 8-13.

3.12 The subject-matter of claims 5-7 would appear to be ***novel.***

4. *Inventive Step* **(Art. 33(3) PCT)**

The subject-matter of claims 5-7 relates to particular AMPA antagonists in combination with carboxamides.
Carboxamides being useful for the treatment of epilepsy is known, see for instance the documents cited under '*novelty*'.
The usefulness of AMPA antagonists for the treatment of epilepsy is known from e.g. **D3** and **D11** to **D17**, as well in combination with carboxamides.
In addition, **D18** discloses that the compounds of *formula I* have AMPA antagonistic properties and thus, due to their anticonvulsive activity, are useful for the treatment of *epilepsy*.
Thus, it cannot be considered that a person skilled in the art would need any special inventive idea to combine compounds of formula I with carboxamides.

An ***inventive step*** can therefore ***not be acknowledged*** for the subject-matter of claims 5-7.

5. *Industrial Applicability* **(Art. 33(4) PCT)**

5.1 The requirements of industrial applicability would be fulfilled for the subject-matter of claims 1-8 and 10-13.

5.2 For the assessment of the present claim 9 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION VI

6. *Certain published documents*

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim) (day/month/year)*
WO 03/042182	22/05/03	11/11/02	12/11/01

WO 03/042182 (**D20**) discloses the usefulness of monohydroxycarbamazepine for the treatment of affective and attention disorders (epilepsy) and the possible combination with e.g. anticonvulsants (e.g. gabapentin).